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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,957	12/04/2001	Shoshana Paglin	AP33710 072734.0121	2771

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EXAMINER	
MCINTOSH III, TRAVISS C	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,957	PAGLIN ET AL.	
	Examiner	Art Unit	
	Traviss C McIntosh	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-52* is/are pending in the application.

4a) Of the above claim(s) *22-32 and 43-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-21 and 33-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed March 23, 2004 has been received, entered into the record, and carefully considered. The following information provided in the amendment affects the instant application by:

Claims 1, 3, 6, 9-11, 13, and 15 have been amended.

Claim 5 has been canceled.

Claims 33-52 have been added.

Remarks drawn to rejections of Office Action mailed September 23, 2003 include:

112 2nd paragraph rejections: which have been overcome by applicant's amendments and have been withdrawn.

102(b) rejection which has been maintained for reasons of record.

103(a) rejection which has been maintained for reasons of record.

An action on the merits of claims 1-4, 6-21, and 33-52 is contained herein below. The text of those sections of Title 35, US Code which are not included in this action can be found in a prior Office action.

It is noted that newly submitted claims 43-52 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims as originally filed comprised methods wherein a cell which was previously exposed to a cytotoxic agent was subsequently contacted with inhibitors of V-ATPase activity. Claims 43-52

are drawn to a method comprising contacting cells with an inhibitor of V-ATPase activity, then contacting the cell with a cytotoxic agent, which is patentably distinct from the methods as originally claimed.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 43-52 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4, 6-14, 16-21, and 33-42 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.*

In the amendment filed on March 23, 2004, applicants have amended independent claims 1 and 13 to include the phrase "prior to an accumulation of acidic vesicular organelles in said cell". Applicants state that support of the recitation can be found on page 8, paragraph 16; page 14, paragraph 34, and pages 16-17, paragraph 40. However, the specification is not seen to be sufficient to support for the claims as amended. Claims 1 and 13 as currently amended are drawn

to a method for promoting cell death of a cell which has been previously exposed to a cytotoxic agent comprising contacting said cell with an inhibitor of vacuolar proton ATPase activity or an agent capable of inhibiting acidic vesicular function or acidification prior to an accumulation of acidic vesicular organelles in said cell. However, the specification is replete with information showing that the surviving cancer cells (those exposed to a cytotoxic agent which survive) accumulate acidic vesicular organelles. The specification is silent to cells which have been previously exposed to a cytotoxic agent which do not comprise acidic vesicular organelles. Applicants point to paragraphs 16, 34, and 40 for support, however, paragraph 16 states:

> The present invention is based, at least in part, on the discoveries that (i) following irradiation surviving **cancer cells accumulate acidic vesicular organelles** (AVOs) and that their acidification is mediated by V-H^+-ATPase, and (ii) **surviving colonies of cells contain higher levels of AVO**.

Paragraph 34 states:

> The present invention is based, at least in part, on the discovery that **irradiation of cancer cells results in the appearance and accumulation of acidic vesicular organelles (AVO)** and that acidification of AVO is decreased by V-H^+-ATPase inhibitors. Such inhibitors also promote the damaging effects of radiation and chemotherapy and result in greater cell death than radiation or chemotherapy alone. **Specifically, it was observed that the progeny of irradiated cells contain increased levels of AVO indicating that the emergence of acidic compartments** serve to protect cells against radiation damage.

Paragraph 40 states:

> The present invention provides for methods and compositions for decreasing cell survival and/or promoting cell death comprising inhibiting V-H^+-ATPase activity and/or function/acidification of AVO, particularly after exposure of the cells to a cytotoxic agent. The cytotoxic agent may be radiation, including x-ray irradiation and particle emission (e.g. from a radioactive seed) or a chemical agent, such as a chemotherapeutic agent used in cancer treatment (adriamycin or etoposide, for example) or hormones such as tamoxifen or other biologicals such as TNF-α or bFGF. The present invention is based, at least in part, on the discovery that **irradiation of cancer cells results in the appearance and accumulation of**

> **acidic vesicular organelles**, i.e., AVO, which are acidified by a V-H^+-ATPase. Inhibition of acidification of these organelles by inhibition of V-H^+-ATPase promotes the damaging effects of the radiation and results in greater cell death than radiation alone.

Applicants do not have support for the claims as amended, specifically for "contacting said cell with an inhibitor of vacuolar proton ATPase activity or an agent capable of inhibiting acidic vesicular function or acidification **prior to an accumulation of acidic vesicular organelles in said cell**". Applicant's disclosure is replete with information which states that the cells which have been previously exposed to cytotoxic agents form vesicular organelles, which serve to protect cells from radiation and chemotherapy damage.

It is noted that a rejection of the claims is reviewable by the Board of Patent Appeals and Interferences.

Additionally, applicants added new independent claim 33 which comprises the phrase "wherein the cytotoxic agent is not stored in acidic organelles of said cell". Applicants then state that support for this recitation can be found at least in the examples, wherein the exemplified cells did not have a cytotoxic agent of the invention stored in acidic vesicular compartments when contacted with an inhibitor of vacuolar proton ATPase activity, wherein applicants then point to the cells of tables 3-11 for support. However, it is noted that tables 3-11 show cells which were irradiated (with a Cs-137 Irradiator – see [0100]) and were then treated with various vacuolar proton ATPase inhibitors. It is noted that although applicants state that the "cytotoxic agent" can be radiation (see [0040]), this is not seen to be sufficient to support a claim which is drawn to "wherein the cytotoxic agent is not stored in acidic organelles of said cell", as the

"cytotoxic agent" (radiation emitted from a Cs-137 irradiator) cannot be stored in a cell. A Cs-137 irradiator emits highly penetrating gamma radiation. Gamma rays are similar to X rays, but X rays generally have lower energy. Gamma radiation is an electromagnetic radiation consisting of waves of energy associated with electric and magnetic fields resulting from the acceleration of an electric charge. Thus, applicants stating that the cells from tables 3-11 do not comprise the cytotoxic agent in their acidic vesicular organelles is not sufficient to support independent claim 33, as the cytotoxic agent from tables 3-11 is radiation, which cannot be stored in the acidic vesicular organelles.

As set forth supra, a rejection of the claims is reviewable by the Board of Patent Appeals and Interferences.

Applicant is required to cancel all new matter in response to these rejections.

Claims 1-4, 6-21, and 33-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for promoting cell death of a cell which has previously been exposed to **adriamycin or irradiation** by contacting said cell with inhibitors of vacuolar proton ATPase activity or inhibitors of acidic vesicular function or acidification, does not reasonably provide enablement for promoting cell death of a cell which has previously been exposed to **cytotoxic agents**. Additionally, while being enabling for the use of **bafilomycins and concanamycins**, does not reasonably provide enablement for **macrolides** (as in claims 6, 17, 36, and 46). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims without undue experimentation.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in ***In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)***. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:
(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims - The nature of the invention

The claims are drawn to a methods of promoting cell death of a cell which has been previously exposed to a cytotoxic agent comprising contacting the cells with inhibitors of vacuolar proton ATPase activity or inhibitors of acidic vesicular function or acidification. Inhibitors of vacuolar proton ATPase activity and inhibitors of acidic vesicular function or acidification are optionally limited to macrolide antibiotics. The cytotoxic agents are limited to "irradiation" and "chemotherapeutic agents".

The state of the prior art

Cytotoxic agents are known on the art to be diverse in structure and function. There is no known therapy which would promote cell death in a cell which has previously been exposed to any cytotoxic agent. Inhibitors of vacuolar proton ATPase activity and inhibitors of acidic vesicular function are known to trigger apoptotic cell death in various cells, such as osteoclasts (as seen by Okahashi et al., "Specific Inhibitors of Vacuolar H^+ -ATPase Trigger Apoptotic Cell Death of Osteoclasts", Journal of Bone and Mineral Research, vol. 12, no. 7, 1997). Macrolide antibiotics are known in the art to be diverse in structure and function from classical macrolides, and bafilomycins and concanamycins are known in the art to be inhibitors of V-ATPases and P-ATPases, as seen by Drose et al. ("Review – Bafilomycins and Concanamycins as Inhibitors of V-ATPases and P-ATPases", The Journal of Experimental Biology, 200, pp. 1-8, 1997).

The level of predictability in the art

The examiner acknowledges the probability and predictability that cell death can be promoted in cells which have been previously exposed to irradiation or adriamycin by contacting cells with inhibitors of V-ATPase activity and inhibitors of acidic vesicular function and that bafilomycins and concanamycins are effective as inhibitors of V-ATPases.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to use the claimed method commensurate in the scope with the instant claims. There is a lack of data and examples which adequately represent the scope of claim as written.

The existence of working examples

The working examples set forth in the instant specification are directed to the use of bafilomycin A1, concanamycin, or salicylihalamide A for promoting death in cells which have been exposed to irradiation or adriamycin.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable promoting cell death of a cell which has previously been exposed to **any cytotoxic agent** by contacting said cell with inhibitors of vacuolar proton ATPase activity or inhibitors of acidic vesicular function or acidification (as in optionally any **macrolide antibiotic**). One skilled in the art could not use the entire scope of the claimed invention without undue experimentation.

Claims 1-4, 11-16, 33-35, 37, and 41-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to a method of promoting cell death wherein a cell is contacted with an inhibitor of V-ATPase activity, which is seen to be missing a critical element. The claim fails to particularly point out the identity of the active agent (compound) to be used in the method

instantly claimed. The current claim language is drawn to the use of an agent in a method wherein the method is not described structurally/formulaically/nomenclatorially; but rather by the agent's mode of action, function or effect requisite to an activity produced when the composition is administered. The claim is missing the critical element, which is the particular or distinct identity of the active agent to be used in the method. Defining the agent to be used in the method structurally, formulaically, or nomenclatorially would be a more preferable way to define the subject matter instead of the current functional description. Independent claims 3, 33, and 43 are rejected for the same reason.

Claim 13 is drawn to a method of promoting cell death wherein a cell is contacted with an agent capable of inhibiting acidic vesicular function or acidification, which is seen to be missing a critical element. The claim fails to particularly point out the identity of the active agent (compound) to be used in the method instantly claimed. The current claim language is drawn to the use of an agent in a method wherein the agent is not described structurally/formulaically/nomenclatorially; but rather by the agent's mode of action, function or effect requisite to an activity produced when the composition is administered. The claim is missing the critical element, which is the particular or distinct identity of the active agent to be used in the method. Defining the agents structurally, formulaically, or nomenclatorially would be a more preferable way to define the subject matter instead of the current functional description. Independent claim 15 is rejected for the same reason.

All claims which depend from an indefinite claim are also indefinite. ***Ex parte Cordova, 10 U.S.P.Q. 2d 1949, 1952 (P.T.O. Bd. App. 1989).***

Claim Rejections - 35 USC § 102

The rejection of claims 1, 2, 4, 6-8, 11-14, and 16-19 under 35 U.S.C. 102(b) as being anticipated by Altan et al. (Document 18 of IDS submitted 2/10/2003) is maintained for reasons of record. New claims 33-38 and 41-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Altan et al. (Document 18 of IDS submitted 2/10/2003).

The claims of the instant application are drawn to the following: claim 1 is drawn to a method of promoting cell death in a cell which has been previously exposed to a cytotoxic agent comprising contacting said cell with an inhibitor of V-ATPase activity. It is noted that the portion of the claims which constitutes new matter, as set forth supra, is not being taken into consideration in the instant rejections. Claim 13 is drawn to a method for promoting cell death in a cell which has been previously exposed to a cytotoxic agent comprising contacting said cell with an agent capable of inhibiting acidic vesicular function or acidification. Dependent claims 2 and 14 limit the cells of claims 1 and 12 to cancer cells. Dependent claims 4 and 16 limit the cytotoxic agent to a chemotherapeutic agent. Dependent claim 6 limits the inhibitor to a macrolide antibiotic. Dependent claim 7 limits the macrolide to bafilomycin A1. Dependent claim 8 limits the inhibitor to concanamycin. Claims 33-38 and 41-42 are correlative to claims 1, 2, 4, 6-8, and 11-12 respectively.

Altan et al. disclose that administering monensin, bafilomycin A1, or concanamycin to a cell which is resistant to adriamycin from previous therapies, sufficiently changes the cells to that of a drug-sensitive cell thereby rendering the cell vulnerable once again to chemotherapy. Thus, Altan teaches to administer the claimed compounds, which are known in the art to be

inhibitors of V-ATPase activity, which is known in the art to promote proton conduction across the vesicle membrane thus inhibit acidification of vesicles, to cells which have been previously treated with a cytotoxic agent (adriamycin, a known chemotherapeutic agent), thereby promoting cell death by once again rendering them vulnerable to chemotherapy (abstract).

Applicant's arguments filed March 23, 2004 have been fully considered but they are not persuasive. Applicant's arguments are drawn to the amendments which were submitted for the claims, however, as set forth supra, applicant's amendments constitute new matter, and thus applicant's arguments are moot.

Claim Rejections - 35 USC § 103

The rejection of claims 9, 10, 20, and 21 under 35 U.S.C. 103(a) as being unpatentable over Altan et al., as set forth supra, in view of Boyd et al. (reference 1 the IDS submitted 2/10/2003) is maintained for reasons of record.

Claims 9 and 20 of the instant application limit the modulator/inhibitor of claims 5 and 13 to a benzolactone enamide, and claims 10 and 21 limit the benzolactone to salicilyhalamide A. (Additionally, as noted in the Office Action dated 3/26/2003, these claims do not receive the priority date of 12/4/2000, but receive a date of 12/4/2001).

Altan et al. teach the method of administering monensin, bafilomycin A1, or concanamycin to a cell which is resistant to adriamycin from previous therapies, sufficiently changes the cells to that of a drug-sensitive cell thereby rendering the cell vulnerable once again to chemotherapy. What is not taught is to administer to a benzolactone enamide or salicilyhalamide A.

Boyd et al. teach that benzolactone enamides, including salicilyhalamide A, are inhibitors of the growth of tumor cells as they inhibit vacuolar proton ATPase activity.

It would have been obvious to one of ordinary skill in the art to administer a compound which has an art recognized activity (inhibit vacuolar proton ATPase activity) for another compound which has the same art recognized activity in a correlative method. Likewise, one of ordinary skill in the art would have a reasonable expectation of success in practicing the method of Altan et al. with the vacuolar proton ATPase inhibitors of Boyd et al. as both compounds are known in the art to have the same effects vacuolar proton ATPase activity. One would be motivated to use the compounds of Boyd et al. in the method of Altan et al. because Altan et al. teaches that inhibitors of vacuolar proton ATPase activity (bafilomycin A1) are effective in resensitizing cells to chemotherapeutic agents after they have been previously treated unsuccessfully with a chemotherapeutic agent, and Boyd et al. teaches that the benzolactone enamides, including salicilyhalamide A, are inhibitors of the growth of tumor cells as they inhibit vacuolar proton ATPase activity.

Applicant's arguments filed March 23, 2004 have been fully considered but they are not persuasive. Applicant's arguments are drawn to the amendments which were submitted for the claims, however, as set forth supra, applicant's amendments constitute new matter, and thus applicant's arguments are moot.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss C McIntosh whose telephone number is 571-272-0657. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Traviss C. McIntosh III
June 2, 2004

James O. Wilson
Art Unit 1623
Supervisory Patent Examiner